# SYNTHESIS OF NOVEL NITROGEN HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST: SULFOXIMINES AND PYRAZOLO[3,4-*b*]PYRIDINE DERIVATIVES

## SYNOPSIS

OF THE Ph.D. THESIS TO BE SUBMITTED

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IN

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BY

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# SYNOPSIS

## Introduction

Nitrogen-based heterocyclic chemistry is a crucial and distinct class in the realm of organic chemistry, with a vast amount of research dedicated to the discovery and development of novel molecules.[1,2] Over the past two decades, there has been a growing interest in these compounds, and they have become a hot topic in medicinal chemistry and chemical science. [2] Researchers have been fascinated with nitrogen-containing heterocycles for many years due to their exceptional ability to interact with biological targets. Nitrogen heterocyclic compounds have shown promising therapeutic properties and the **Figure 1** demonstrates the increasing interest in nitrogen heterocyclic chemistry by showcasing the advancements made in SciFinder$^n$ since the 1950s. The graph reveals a steady increase in the number of publications related to nitrogen heterocycles, indicating their continued significance in scientific research.

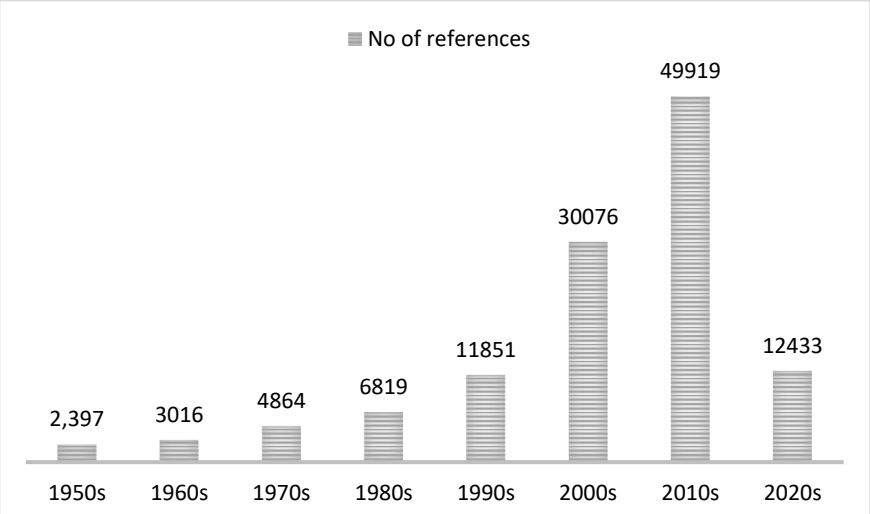



**Figure 1**. Publications on nitrogen-based heterocycles since 1950s (Source: SciFinder$^n$)

Many *N*-heterocyclic compounds that are broadly distributed in nature, possess physiological and pharmacological properties and are constituents of many biologically important molecules,[3] including many vitamins,[4] nucleic acids,[5] pharmaceuticals,[6] antibiotics,[7] dyes,[8] and agrochemicals,[9] amongst many others.[10] The base pairs of DNA and RNA (guanine, cytosine, adenine, and thymine) are also made up of *N*-heterocyclic compounds, namely purines, pyrimidines, etc. Furthermore, the electron-rich nitrogen heterocycle is not only able to readily accept or donate a proton, but it can also easily establish diverse weak interactions. Some of

these intermolecular forces, such as like hydrogen bonding formation, dipole-dipole interactions, hydrophobic effects, van der waals forces and π-stacking interactions of nitrogen compounds have increased their importance in the field of medicinal chemistry and allows them to bind with a variety of enzymes and receptors in biological targets with high affinity due to their improved solubility.[5] The structural features of their derivatives are beneficial since they exhibit broad bioactivities. A glance at the FDA databases reveals that nearly 75% unique small-molecule drugs contain a nitrogen heterocycle.[11]

Particularly, the utility of *N*-containing heterocyclic structures with five-, six- and seven-membered rings are key motifs in medicinal chemistry and chemical science.[12,13] Therefore, the development of heterocycles as scaffolds containing a high degree of diversity has become a major focus in modern active ingredient discovery. Five-membered triazolidine-3,5-diones (urazoles), six-membered triazine-2,4-diones containing heterocyclic derivatives are privileged structures for drug design and in crop science discovery.[14,15]

In this background, we have aimed to design new synthetic strategies for the synthesis of dihydro triazine-2,4-diones (**2**) from triazolidine-3,5-diones (**1**) *via* N–N bond cleavage followed by intramolecular ring closure. Similarly, we studied the rearrangement of fused bicyclic compounds (**3**) into a new class of N–C bridge head heterocycles fused with saturated ring systems (**4**) as shown in the **Figure 2** and studied their biological activity towards crop-protection.

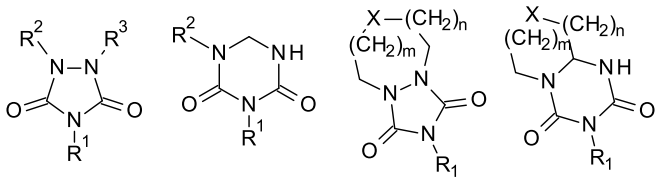


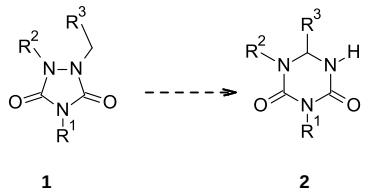

**Figure 2.** General structures of monocyclic, bicyclic triazolidine-3,5-diones and dihydro triazine-2,4-diones

The thesis entitled "**Synthesis of Novel Nitrogen Heterocyclic Compounds of Biological Interest: Sulfoximines and Pyrazolo[3,4-*b*]pyridine Derivatives**" has been classified into the following five chapters with subsections in each chapter.

# Chapter 1: Introduction to nitrogen heterocycles

Chapter 1 explores the importance of nitrogen heterocycles and their synthesis. Nitrogen heterocycles molecules find widespread applications in fields like medicine, agriculture, and material science, making their synthesis a critical area of study. One such method for synthesizing nitrogen heterocycles involves 1,2-rearrangement reactions, which entail the migration of a substituent from one position to another in the heterocycle ring. Especially, the migration of atom or group from one hetero atom to an adjacent carbon has valuable applications for the synthesis of various complex nitrogen heterocycles.

In these 1,2-rearrangement reactions, N–N fragmentation and cyclization is migration of a group from hetero atom to adjacent carbon, which is also an atom-economical method. This method involves breaking the N–N bond in a heterocycle and utilizing the resulting fragments to create a novel heterocycle ring system. This technique holds the potential to provide a more cost-effective and efficient approach to synthesizing novel nitrogen heterocycles. As a result of this research, the hypothesis emerged that trazolidine-3.5-diones **1** could be transformed into triazinane-2,4-diones **2** through N–N fragmentation, followed by cyclization as shown in **Scheme 1**.




1 2

**Scheme 1.** Hypothesis for the syntehsis of triazinane-2,4-diones from urazoles

# Chapter 2: Synthesis of symmetrical and unsymmetrical *N,N'*-diakyl triazolidine-3,5-diones

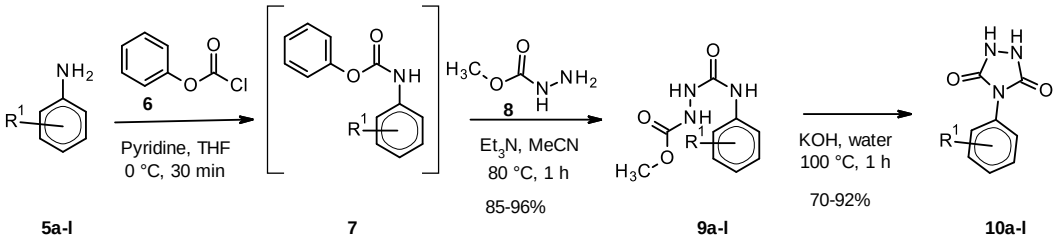
## 2.1. A brief review on triazolidine-3,5-diones

This is an introductory section, which deals with a brief account of synthesis, applications, and biological activities of triazolidine-3,5-diones based on prior art in this domain.

## 2.2. Synthesis of monosubstituted triazolidine-3,5-diones

This section deals with the synthesis and characterization of some monosubstituted triazolidine-3,5-dione derivatives.

Our synthetic strategy focused on the construction of the triazolidine-3,5-dione ring system. Initially, efforts were focused on one pot synthetic methods, but those efforts ended with either no product or only lower yields to achieve triazolidine-3,5-diones.[16] Hence, we tried a 3-step synthesis starting with simple and commercially available anilines **5a-l**. Several reaction conditions and reagents were screened, and triazolidine-3,5-diones synthesis was accomplished by reacting aniline derivatives with phenyl chloroformate **6** to produce phenyl carbamate derivatives **7**. Following that, reaction with methyl carbazate **8** to get semi carbazides **9a-l**, which cyclized into monosubstituted triazolidine-3,5-diones **10a-l** in good to excellent yields as shown in **Scheme 2**. The scope of reaction and compounds prepared are shown in **Figure 3** & **Figure 4**.




**Scheme 2**. Synthesis of monosubstituted triazolidine-3,5-diones **10a-l**.

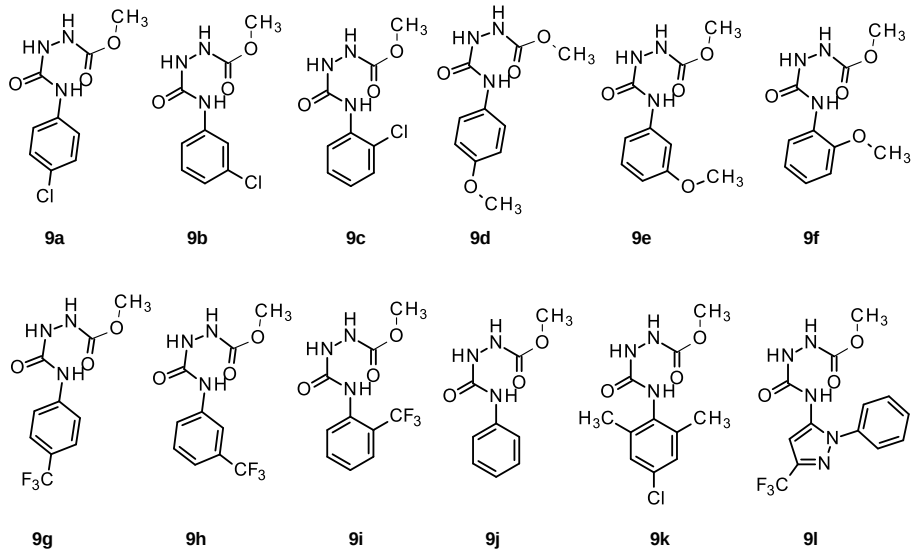



**Figure 3.** Substrates scope of semicarbazide derivatives

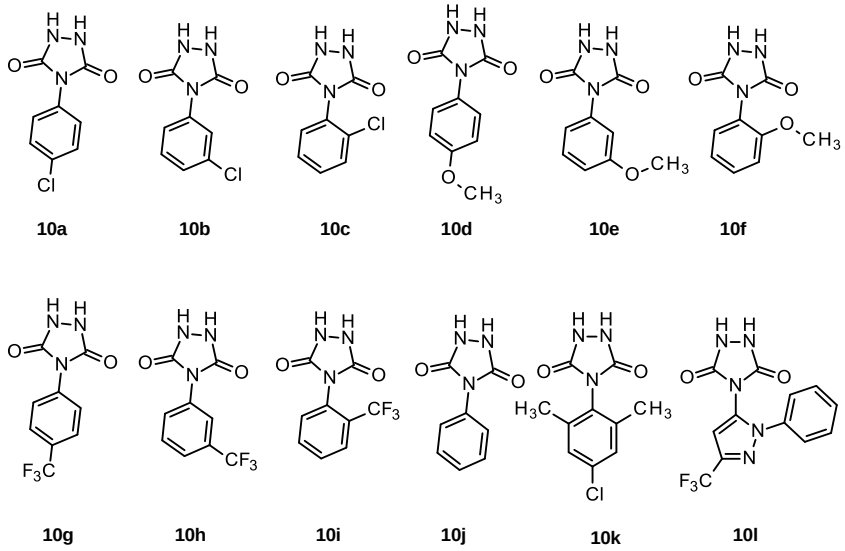
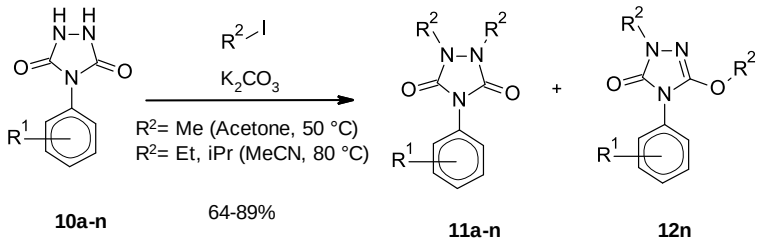



**Figure 4.** Substrates scope of monosubstituted triazolidine-3,5-diones

### 2.3. Synthesis of symmetrical *N,N'*-dialkyl triazolidine-3,5-diones

This section deals with the synthesis and characterization of some new tri-substituted symmetrical triazolidine-3,5-dione derivatives.

Tri-substituted triazolidine-3,5-diones **11a-n** were synthesised by dialkylation of mono substituted triazolidine-3,5-diones **10a-l** under base mediated conditions. When 4-aryl-1,2,4-triazolidine-3,5-diones **10a-l** were reacted with a primary alkyl halide using $K_2CO_3$ in acetone at 50 °C, the reaction was fully completed in 3 to 5 hours with excellent yields of symmetrical trisubstituted 4-aryl-1,2,4-triazolidine-3,5-diones **11a-n** as depicted in **Scheme 3**. However, dialkylation using secondary alkyl halide in acetonitrile at 80 °C resulted *N,O*-alkylated product as major product **12n** along with symmetrical *N,N'*-dialkyl product **11n** as minor.




**Scheme 3.** Synthesis of symmetrical *N,N'*-dialkyl 4-(aryl)-1,2,4-triazolidine-3,5-diones

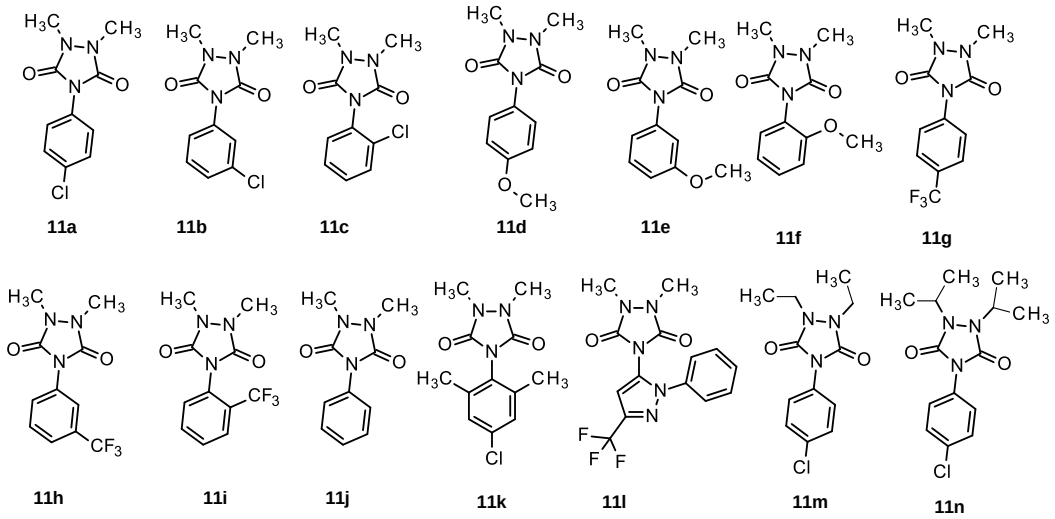
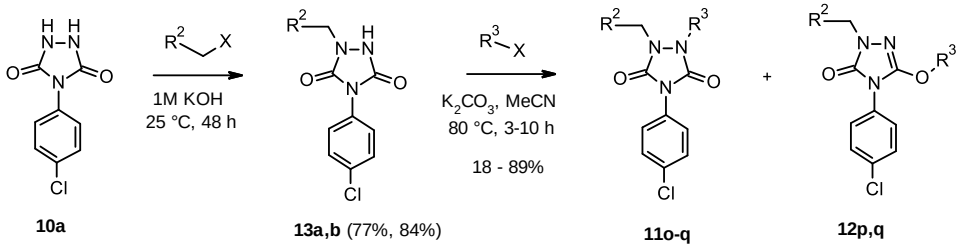



**Figure 5.** Substrate scope of trisubstituted symmetrical triazolidine-3,5-diones

### 2.4. Synthesis of unsymmetrical *N,N'*-dialkyl triazolidine-3,5-diones

This section deals with the synthesis and characterization of some tri-substituted unsymmetrical triazolidine-3,5-dione derivatives.

For the synthesis of unsymmetric *N,N'*-dialkylated 4-aryl-1,2,4-triazolidine-3,5-diones, a different strategy was used. Unsymmetric *N,N'*-dialkylated 4-aryl-1,2,4-triazolidine-3,5-diones (**11o – 11q**) were prepared from 4-(4-chlorophenyl)-1,2,4-triazolidine-3,5-dione **10a** in two step synthesis as shown in **Scheme 4**. Mono *N*-alkylation was performed by reacting with alkyl halide in 1M KOH solution at 25 °C. A second alkylation was then performed using alkyl halide, $K_2CO_3$ in acetonitrile at 80 °C. In particular, it was observed that when the second alkylation was conducted using secondary alkyl halide, the formation of the *N,O*-alkylation products **12p,q** was predominant to the *N,N'*-dialkylation products **11p,q**.




**Scheme 4.** Synthesis of unsymmetrical *N,N'*-dialkyl triazolidine-3,5-diones

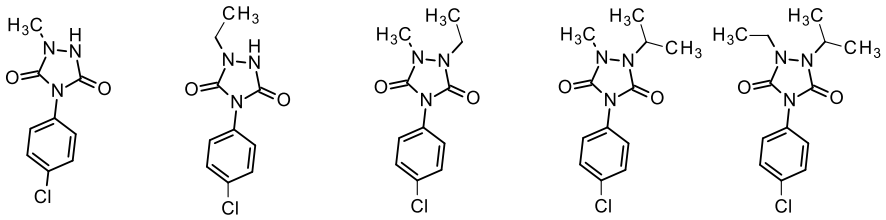



**Figure 6.** Substrate scope of unsymmetrical di- and trisubstituted triazolidine-3,5-diones

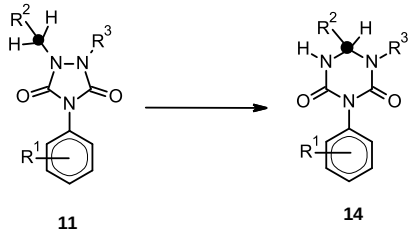
# Chapter-3: Synthesis of dihydro triazine-2,4-diones and their derivatives

## 3.1. A brief review on dihydro triazine-2,4-diones and their derivatives

This is an introductory section, which deals with a brief account of synthesis, applications, and biological activities of triazine-2,4-diones and their derivatives based on publications appearing in literature up to date.

## 3.2. Synthesis of dihydro triazine-2,4-diones via N–N fragmentation of triazolidine-3,5-diones

We were interested to develop a method to synthesize dihydro triazine-2,4-dione derivatives, we reasoned that an N–N fragmentation[17,18] of a triazolidine-3,5-dione ring could lead to the construction of the six-membered dihydro triazine-2,4-dione ring system through an intramolecular ring closure, while ensuring complete atom economy, as depicted in **Scheme 5**.

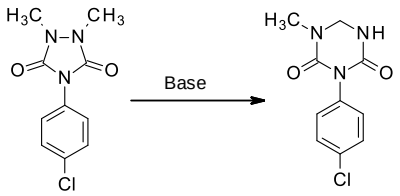



**Scheme 5.** Synthesis of dihydro triazine-2,4-diones *via* fragmentation-cyclization approach

We began our studies by examining **11a** ($R^1$ = 4-Cl) as model reactant. Initial studies were focused on screening different bases to promote the designed fragmentation-cyclization reaction (**Table 1**). A few usual bases were tested under thermodynamic reaction conditions (25 °C to 100 °C) for their ability to promote the desired reaction. In case of bases like NaH, *t*BuOK, and $NaNH_2$, no desired reaction was observed to yield product **14a** (**Table 1**, entries

1-3). The use of *n*-BuLi at –78 °C to 0 °C in hexane, with or without TMEDA did not lead to the desired reaction (**Table 1**, entries 4,5). When *n*-BuLi was replaced by 2 equiv. of lithium bis(trimethylsilyl)amide (LiHMDS) as a base, at –78 °C, once again the reaction did not proceed. However, when the reaction mixture was brought to 25 °C, traces of the formation of **14a** was observed and when the reaction was heated to 50 °C for 8 h, a 16% isolated yield of **14a** was obtained (**Table 1**, entry 7). The product was purified by column chromatography to isolate pure compound **14a**. The resulting dihydro triazine-2,4-dione **14a** was characterized by using $^{1}$H NMR, $^{13}$C NMR, HRMS and a single X-ray analysis. Further optimizations were then investigated; by performing the reaction with lithium diisopropylamide (LDA) as the base in tetrahydrofuran at 25 °C, a yield of 55% of **14a** was obtained (**Table 1**, entry 8). In hydrocarbon solvents (**Table 1**, entries 9-11), yields of **14a** were enhanced to 65%. We observed an acceleration in reaction rate with temperature, and we noted that at least 1.5 equiv. of base are required for complete conversion of **11a** to afford optimal yield (**Table 1**, entries 11-14).

**Table 1:** Optimization of rearrangement reaction

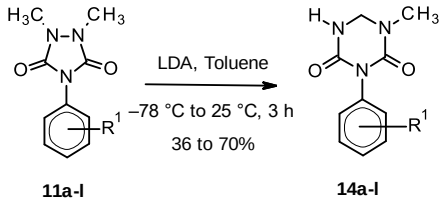



**11a** **14a**

| Entry | Base (equiv.) | Solvent | Temperature °C | Time h | % Yield of 14a |
|---|---|---|---|---|---|
| 1 | NaH (1.5) | NMP | 25 to100 | 7 | 0 |
| 2 | *t*BuOK (1.5) | NMP | 25 to 100 | 7 | 0 |
| 3 | $NaNH_2$ (1.5) | toluene | 25 to 100 | 7 | 0 |
| 4 | *n*-BuLi (1.1), TMEDA (1.1) | THF | –78 to 0 | 3 | 0 |
| 5 | *n*-BuLi (2.0) | heptane | –78 to 0 | 3 | 0 |
| 6 | *n*-BuLi (2.0), TMEDA (2.0) | heptane | –78 to 0 | 3 | 0 |
| 7 | LiHMDS (2.0) | THF | –78 to 50 | 8 | 16 |
| 8 | LDA (2.0) | THF | –78 to 25 | 5 | 55 |
| 9 | LDA (2.0) | toluene | –78 to 25 | 3 | 65 |

| | | | | | |
|---|---|---|---|---|---|
| 10 | LDA (2.0), | hexane | –78 to 25 | 3 | 64 |
| 11 | LDA (2.0) | heptane | –78 to 25 | 3 | 65 |
| 12 | TMPLi (2.0) | toluene | –78 to 25 | 3 | 65 |
| 13 | LDA (1.0) | toluene | –78 to 25 | 3 | 58 |
| 14 | LDA (1.5) | toluene | –78 to 25 | 3 | 65 |
| 15 | LDA (2.5) | toluene | –78 to 25 | 3 | 64 |
| 16 | LDA (2.0) | toluene | –78 to 0 | 8 | 65 |

The conditions (**Table 1**, entry 14) were then used to examine the scope of substituents tolerated on the aryl ring, as indicated in **Scheme 6**. The reaction is tolerant of electron donating and electron withdrawing substituents **14a-l**. We also investigated steric effects, and found that the presence of one, or even two ortho substituents on the aryl ring did not negatively impact the yields obtained (**14i** and **14k)**. These results underline the robustness of this approach. All products were isolated in pure form by triturating with ethyl acetate.




**Scheme 6.** Synthesis of dihydro triaine-3,4-diones **14a-l** from *N,N'*-dimethyl urazoles **11a-l**

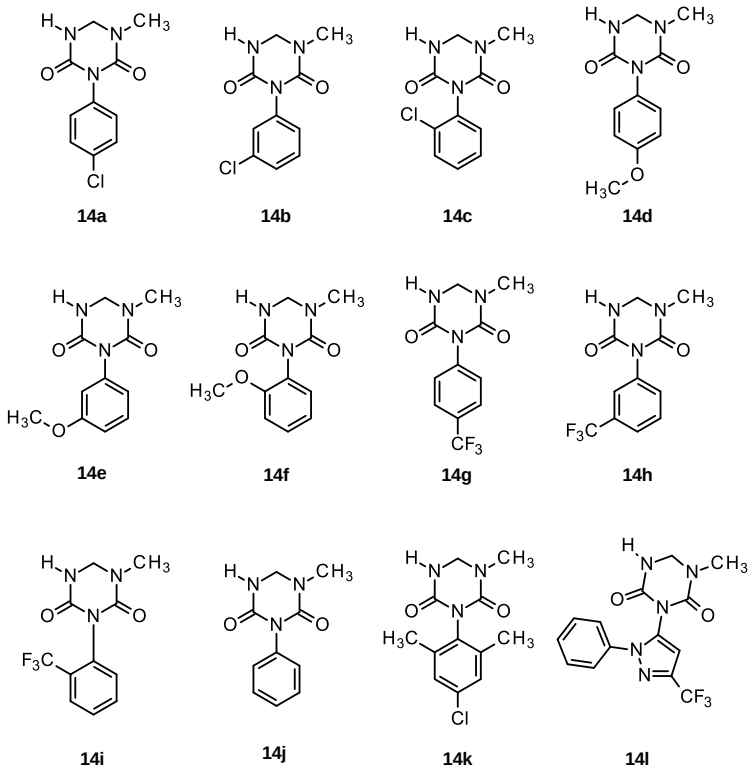
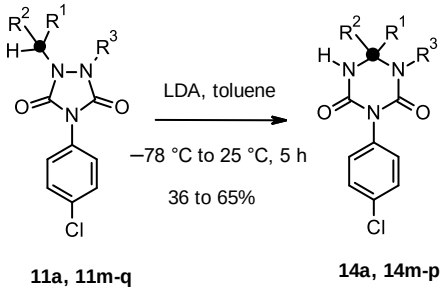



**Figure 7.** Substrate scope of dihydro triazine-2,4-dione derivatives

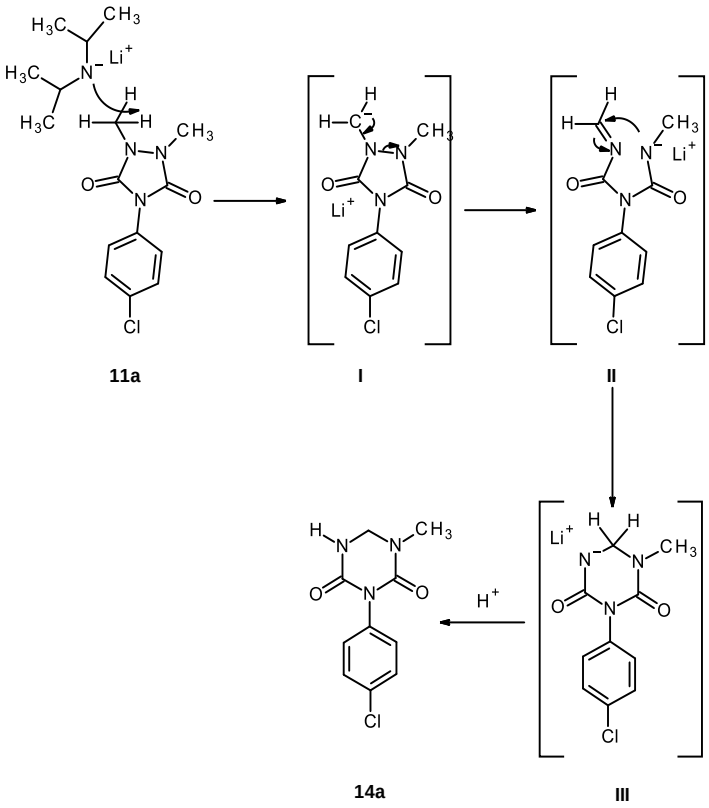
Next, we planned to study the steric effect of differently substituted *N,N'*-dialkyl urazole rearrangement. Symmetrical *N,N'*-dialkyl urazoles were treated with LDA, rearrangement of the primary dialkylated, substrates such as *N,N'*-dimethyl and *N,N'*-diethyl triazolidine-3,5-diones (**11a** and **11m)** under standard conditions gave good yields of **14a** and **14m**. Unsymmetrical *N,N'*-dialkylated triazolidine-3,5-diones **11o** and **11p** were then treated with LDA and exclusively the isomers **14o** and **14p** were isolated in moderate yields as shown in **Table 2**. The sterically hindered substrate **11q** rearranged to **14q** and isolated in lower yield. However, when *N,N'*-diisopropyl substituted urazoles **11n** failed to deliver rearranged product, because the steric hindrance of isopropyl groups did not facilitate intramolecular cyclization.

**Table 2.** Steric effect on rearrangement reaction



| Entry | Starting material | | | | Product | | | | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| | **11** | $R^1$ | $R^2$ | $R^3$ | **14** | $R^1$ | $R^2$ | $R^3$ | |
| **1** | **11a** | H | H | $CH_3$ | **14a** | H | H | $CH_3$ | 65 |
| **2** | **11m** | H | $CH_3$ | $C_2H_5$ | **14m** | H | $CH_3$ | $C_2H_5$ | 65 |
| **3** | **11n** | $CH_3$ | $CH_3$ | $CH(CH_3)_2$ | **14n** | $CH_3$ | $CH_3$ | $CH(CH_3)_2$ | 0 |
| **4** | **11o** | H | H | $C_2H_5$ | **14o** | H | H | $C_2H_5$ | 47 |
| **5** | **11p** | H | H | $CH(CH_3)_2$ | **14p** | H | H | $CH(CH_3)_2$ | 43 |
| **6** | **11q** | H | $CH_3$ | $CH(CH_3)_2$ | **14q** | H | $CH_3$ | $CH(CH_3)_2$ | 36 |

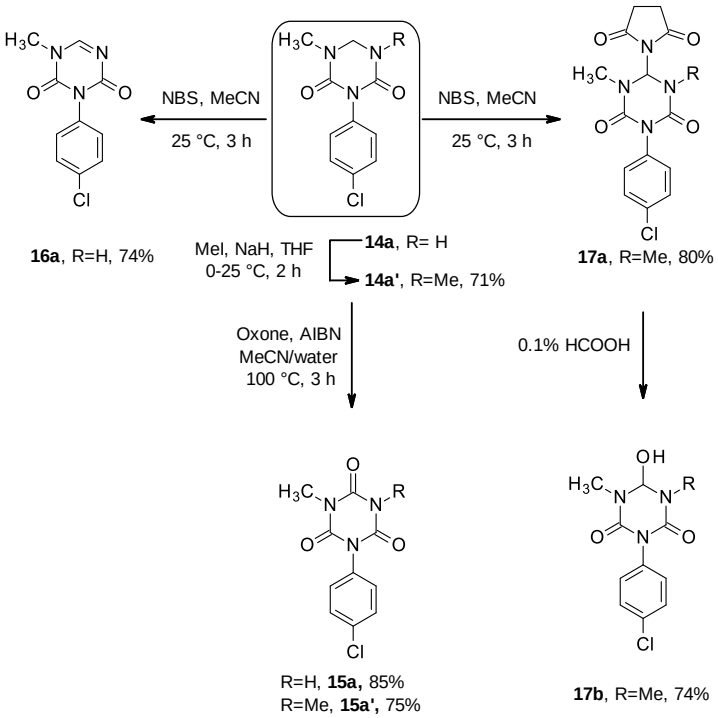
Based on available literature[17,18] a plausible pathway for the synthesis of substituted unsymmetrical dihydro triazine-2,4-diones is outlined in **Scheme 7**; the first step involves a deprotonation of **11a** by the base LDA with the resulting anion undergoing a ring fragmentation through cleavage of the N–N bond leading to imine–urea anion intermediate **II**. This intermediate **II** undergoes an intramolecular cyclization through nucleophilic addition of the urea nitrogen onto the imine leading to the six membered ring intermediate **III**, protonation of which gives **14a** (**Scheme 7**).




**Scheme 7.** Plausible mechanism for fragmentation-cyclization

### 3.3. Reactivity of dihydro triazine-2,4-diones

We were keen to explore the reactivity of dihydro triazine-2,4-dione ring systems. Simple alkylation of **14a** using methyl iodide and sodium hydride in tetrahydrofuran gave the trisubstituted 1,3,5-triazine-2,4-dione **14a'** in 71% yield. This method enables us to access novel 1,3,5-trisubstituted dihydro triazine-2,4-diones. Furthermore, **14a** and **14a'** could be used as synthons to access the di- and trisubstituted triazine-2,4,6-triones **15a** and **15a'** using simple oxidative methods with Oxone in the presence of AIBN in good yields as shown in **Scheme 8**.

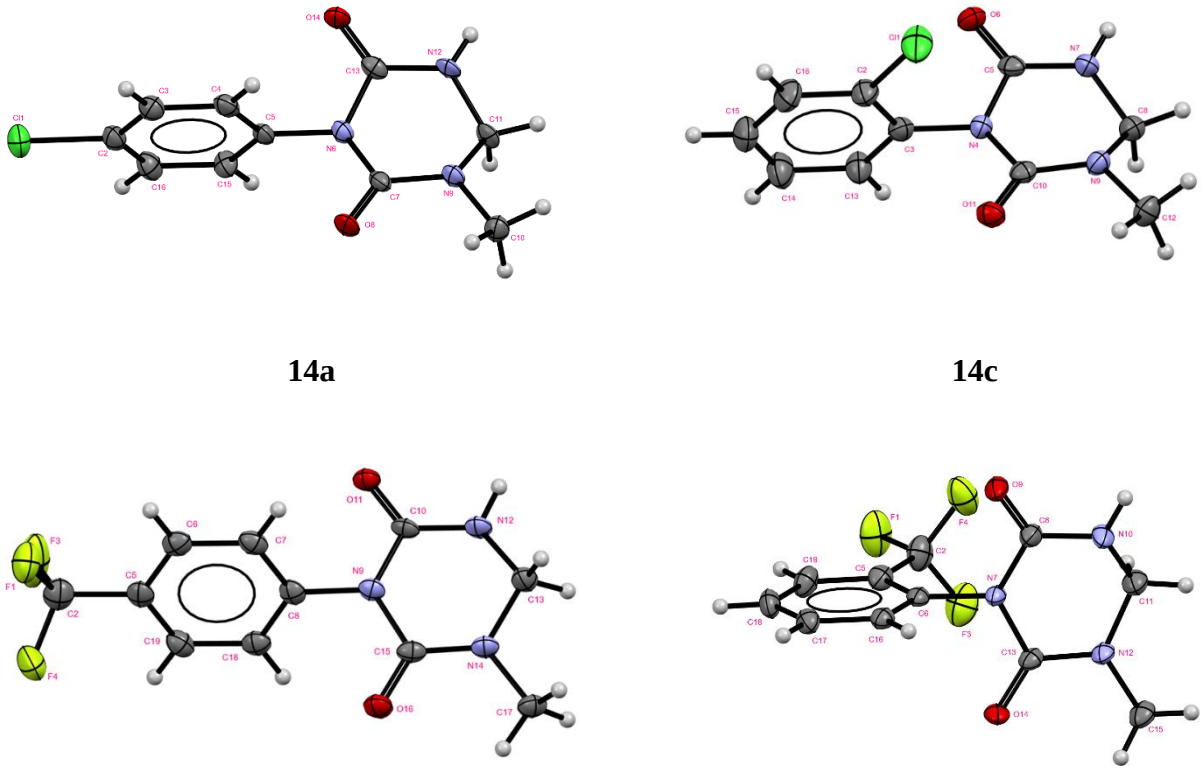



**Scheme 8.** Synthesis of substituted triazine-2,4,6-triones and triazine-2,4-diones.

Bromination of **14a** using NBS as the brominating agent led to our surprise to the triazine-2,4-dione **16a** in 74% yield (**Scheme 8**). However, under the same condition bromination of **14a'** yielded **17a** in 80% yield, in which addition of succinimide to an amidinium intermediate led to a new C–N bond formation. Hydrolysis of **17a** using mild acid (0.1% formic acid) yielded the hydroxylated product **17b** in 74% (**Scheme 8**).

### 3.4. Analysis of triazine-2,4-dione derivatives

All compounds synthesized were characterized by IR, NMR and HRMS analysis. Additionally, compounds **14a**, **14c, 14g** and **14i** were examined by single crystal X-ray diffraction to confirm the exact structure beyond doubt (**Figure 8**).



**14a** **14c**

**14g** **14i**

**Figure 8.** ORTEP representation of **14a, 14c, 14g** and **14i** with thermal ellipsoids shown at the 50% probability level. Hydrogen atoms of arbitrary size.

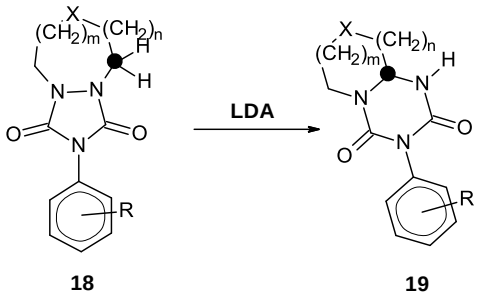
## Chapter 4: Synthesis of N–C fused bicyclic 1,3,5-triazinane-2,4-diones

### 4.1. A brief review on bicyclic 1,3,5-triazinane-2,4-diones

This is an introductory section, which deals with a brief account of synthesis, applications, and biological activities of bicyclic 1,3,5-triazinane-2,4-diones heterocycles on publications from literature search.

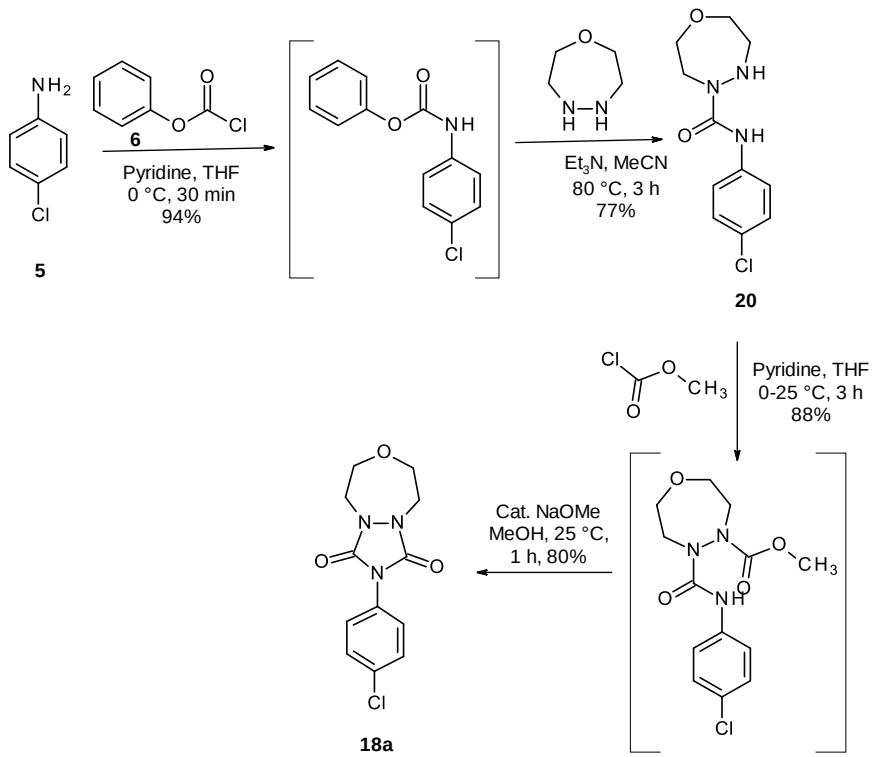
### 4.2. Synthesis of bicyclic triazolidine-3,5-diones

We were interested to develop a method to synthesize fused bicyclic 1,3,5-triazinane-2,4-dione, we reasoned that an N–N fragmentation[17,18] of a fused urazoles could lead to the construction of N–C fused ring system through an intramolecular ring closure, while ensuring complete atom economy, as depicted in **Scheme 9**.




**Scheme 9.** Synthesis of N–C fused heterocycles

Firstly, we planned to synthesize bicyclic urazoles in multistep step synthesis from anilines as shown in the **Scheme 10**. Bicyclic urazole **18** was achieved by reacting aniline **5a** with phenyl chloroformate to produce phenyl carbamate derivatives. Following that, reaction with cyclic hydrazine yielded carbazate **20**, which further treated with methyl chloroformate to give semi carbazide, which further cyclized into bicyclic urazole **18a** in good yield as shown in **Scheme 10**.

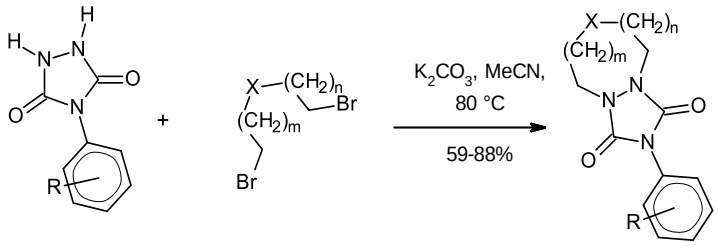



**Scheme 10.** Synthesis of bicyclic urazoles from anilines

Further, we planned to develop a simple, efficient approach for the synthesis of different bicyclic triazolidine-3,5-diones **18** in a single step using triazolidine-3,5-dione **11a** (R = 4-Cl) as shown in **Table 3.** Bicyclic triazolidine-3,5-diones of varying ring size were prepared by the

alkylation of triazolidine-3,5-dione **11a** with dibromo alkane **21** using potassium carbonate as a base in acetonitrile at reflux temperature to yield bicyclic triazolidine-3,5-diones **18a-c** in 52-88% yields. The length of the carbon chain in the dibromo alkanes had no significant impact on the yields. Also, the same method was used to prepare oxadiazepine fused bicyclic triazolidine-3,5-dione derivatives using commercially available 1-bromo-2-(2-bromoethoxy)ethane as an alkylating reagent to obtain perhydro triazolo[1,2-*d*][1,4,5]oxadiazepine-1,3-diones **18d-f** in moderate to good yields by reaction with triazolidine-3,5-diones **11a**, **11f**, and **11i** (**Table 3**, entries 4-6).

**Table 3.** Synthesis of oxa-, thiadiazapene and triazepine fused urazoles

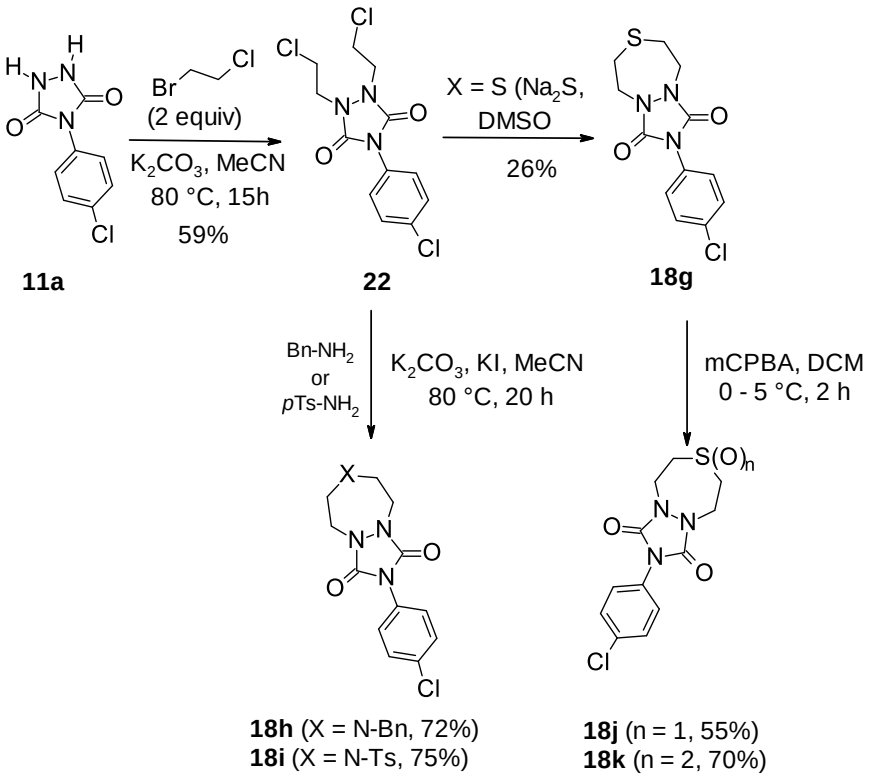



**11a,f,i** **21** **18a-f**

| S. No. | Starting material (**11**) | Dibromo alkane **21** | | | Reaction time | Product **18** (% of yield) |
|---|---|---|---|---|---|---|
| | R | X | m | n | | |
| 1 | 4-Cl (**11a**) | C | 1 | 1 | 9 h | **18a** (84%) |
| 2 | | C | 0 | 1 | 5 h | **18b** (88%) |
| 3 | | C | 0 | 0 | 6 h | **18c** (82%) |
| 4 | | O | 1 | 1 | 6 h | **18d** (75%) |
| 5 | 2-$CF_3$ (**11f**) | O | 1 | 1 | 5 h | **18e** (59%) |
| 6 | 2-OMe (**11i**) | O | 1 | 1 | 5 h | **18f** (68%) |

A complimentary approach was used to prepare bicyclic triazolidine-3,5-diones containing a sulphur and nitrogen atom X by reacting triazolidine-3,5-dione **11a** with two equiv. of 1-bromo-2-chloro ethane in acetonitrile at 80 °C to yield the bis-dichloro-ethyl triazolidine-3,5-dione **22** in 59%, which was then treated with sodium sulphide in dimethyl sulfoxide at 80 °C to yield tetrahydro-[1,2,4]triazolo[1,2-*d*][1,4,5]thiadiazepine-1,3-dione **18g** in 26% yield (**Scheme 11**). However, the reaction of compound **22** with benzylamine and *p*-toluene

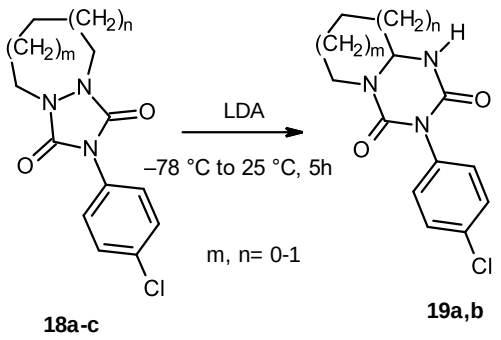
sulphonamide in acetonitrile at 80 °C gave compound **18h** and **18i** in good yields, **Scheme 11**. Further, controlled oxidation of compound **18g** using mCPBA as oxidant yielded **18j** and **18k**.




**Scheme 11.** Synthesis of thiadiazapene and triazepine fused urazole.

### 4.3. Synthesis of trazine-2,4-diones bicyclic systems

Next our efforts were focused on the rearrangement of different bicyclic triazolidine-3,5-diones to obtain N–C ring junction dihydro-triazine-2,4-dione bicyclic systems. We began our investigation to study the effect of ring size on the rearrangement as shown in **Scheme 12**. Firstly, the seven membered fused triazolidine-3,5-dione tetrahydro-[1,2,4]triazolo[1,2-*a*]diazepine-1,3-dione **18a** was treated with LDA at –78 °C and slowly brought to 25 °C, stirred for 5 hours to yield hexahydro pyrido[1,2-*a*][1,3,5]triazine-2,4-dione **19a** in 52% yield (**Figure 9**). The structure of compound **19a** was confirmed by $^{1}$H NMR, $^{13}$C NMR and HRMS.




**Scheme 12.** Synthesis of N–C bridge head heterocycles

With these results in hand tetrahydro-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3-dione **18b** was treated under the standard conditions to yield tetrahydro-1H-pyrrolo[1,2-*a*][1,3,5]triazine-2,4-dione **19b** in a comparable yield (**Figure 9**). However, when dihydro pyrazolo[1,2-*a*][1,2,4]triazole-1,3-dione **18c** was treated with LDA, the reaction did not provide the desired product. Instead, the rearrangement of bicyclic triazolidine-3,5-diones was successful to deliver bicyclic 1,3,5-triazinane-2,4-diones in varied ring sizes. However, the rearrangement of a five membered bicyclic triazolidine-3,5-dione was not successful.

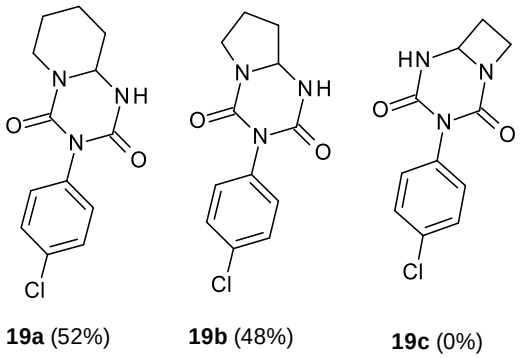
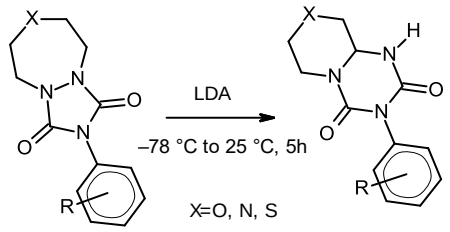



**Figure 9.** Rearrangement reaction products in different ring sizes

After studying the scope of rearrangement reaction with varied carbocyclic ring sizes, we were prompted to see if this method could be extended to the preparation of bridgehead nitrogen heterocycles bearing an additional heteroatom. We concentrated our investigations on seven membered bicyclic triazolidine-3,5-diones bearing a heteroatom X. The rearrangement of 4-Cl substituted phenyl containing tetrahydro-[1,2,4]triazolo[1,2-*d*][1,4,5]oxadiazepine-1,3-dione **18d** was attempted under similar conditions using LDA to obtain the product tetrahydro-[1,4]oxazino[4,3-*a*][1,3,5]triazine-2,4-dione **19d** (**Table 4**, entry 1). Subsequently, with an electron withdrawing group (trifluoromethyl) or an electron donating group (methoxy) at the

ortho position of the aryl ring in tetrahydro-[1,2,4]triazolo[1,2-*d*][1,4,5]oxadiazepine-1,3-dione compounds **18e** and **18f** were treated with LDA under standard condition, but the reaction did not proceed >10% by HPLC. When excess base was added into the reaction, observed bicyclic ring open products. Further, we extended our investigations in bicyclic systems of thiadiazepine and triazepine fused triazolidine-3,5-diones. When tetrahydro-[1,2,4]triazolo[1,2-d][1,4,5]thiadiazepine-1,3-dione **18g** and tetrahydro-[1,2,4]triazolo[1,2-*a*][1,2,5]triazepine-1,3-dione **18h** were treated under standard conditions to afford tetrahydro-1H-[1,4]thiazino[4,3-*a*][1,3,5]triazine-2,4-dione **19g** in 47% yield and tetrahydro-1H-pyrazino[1,2-*a*][1,3,5]triazine-2,4-dione **19h** yielded in 45%, **Table 4**. However, rearrangement of bicyclic urazoles **18i, 18j** and **18k** were failed to give desired reaction.

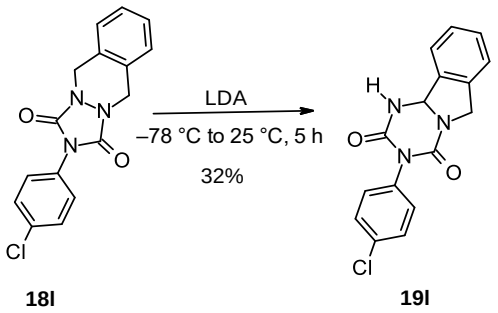
**Table 4.** Rearrangement of oxa-, thiadiazepine, and triazepine fused urazoles




**18d-h** **19d-h**

| S. No. | Starting material **18** | R | X | Product **19 (**% of yield)[a] |
|---|---|---|---|---|
| 1 | **18d** | 4-Cl | O | **19d** (57%) |
| 2 | **18g** | 4-Cl | S | **19g** (47%) |
| 3 | **18h** | 4-Cl | *N*–$CH_2$Ph | **19h** (45%) |

We were keen to see if this approach could be used to prepare tricyclic bridgehead nitrogen heterocycles. triazolidine-3,5-dione **18l** was prepared in 52% yield by the reaction of **11a** with 1,2-bis(bromomethyl)benzene in acetonitrile using $K_2CO_3$ as a base. Rearrangement of dihydro-[1,2,4]triazolo[1,2-*b*]phthalazine-1,3-dione derivative **18l** under the standard conditions yielded dihydro-[1,3,5]triazino[2,1-*a*]isoindole-2,4-dione **19l** in 32% yield and 35% of unreacted starting material compound **18l** was recovered after column purification, **Scheme 13**.




**Scheme 13.** Rearrangement of fused tricyclic triazolidine-3,5-diones

These rearrangement reactions not only offer a wide substrate scope with various electronic and steric substituents on the aryl ring, but also a varied range of saturated ring sizes to deliver bridgehead nitrogen heterocycles, which could provide a novel approach for the synthesis of a variety of complex N–C fused frameworks to search for molecules with potential biological activity.

# Chapter 5: Biological evaluation of nitrogen heterocycles

## 5.1. Introduction to biological evaluation methods

Triazolidine-3,5-diones and triazine-2,4-diones derivatives are interesting compounds with diverse chemical properties and pharmacological activities.[14,15] The newly synthesized compounds were also screened and compared for their biological activities in the field of crop protection. To check the spectrum and potency of the agrochemical activity, some of the compounds were tested against key plant pathogens in the Disease Control Discovery Early Screen, key insect pests in Insecticide Discovery Early Screen and key weed species in Herbicide Discovery Early Screen tested for their crop protection potential. For all screens, data were recorded for replicates and averaged.

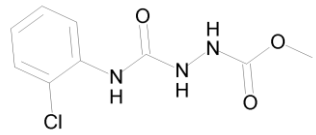
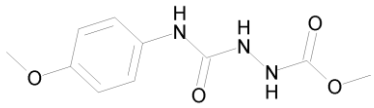
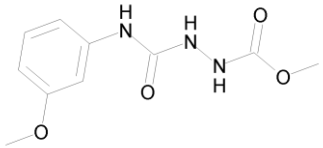
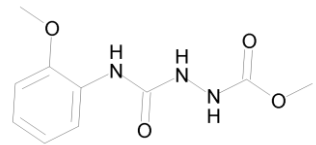
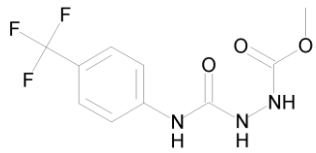
This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of synthesized compounds. Some of triazolidine-3,5-diones, triazine-2,4-dione, bicyclic triazolidine-3,5-diones and bicyclic triazine-2,4-dione compounds showed faint herbicidal activity against *septoria tritici* (septoria leaf blotch) and herbicidal activity against *arabidopsis* and *poaan species.*

% Scores are given for numbered replicates alongside average scores for the replicates (avg.)

| | |
|---|---|
| 0-29 | No colour |
| 30-49 | Yellow colour |
| 50-70 | Green colour |
| 71-100 | Blue colour |

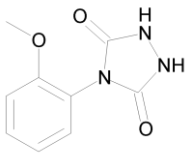
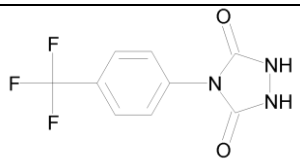
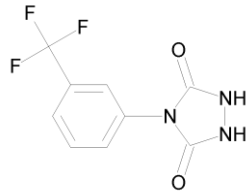
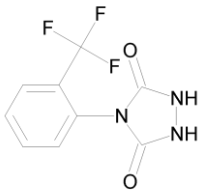
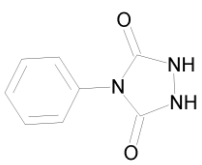
## 5.2. Biological evaluation of semi carbazides

This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of semi carbazides. Herbicidal activities of some semi carbazides are tabulated below:

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| Structure | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **9c** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **9d** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **9e** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **9f** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **9g** | 0 | 0 | 0 | 0 | 50 | 25 |

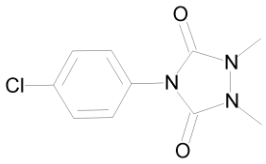
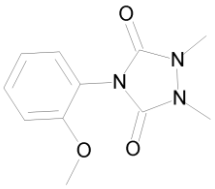
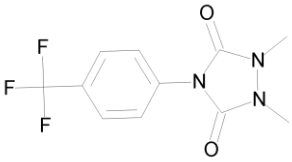
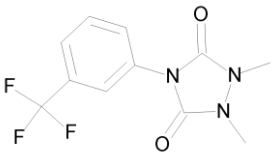
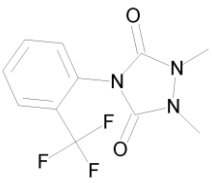
### 5.3. Biological evaluation of monosubstituted triazolidine-3,5-diones

This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of monosubstituted triazolidine-3,5-dione derivatives. Herbicidal activities of some monosubstituted triazolidine-3,5-diones are tabulated below:

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| Structure | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **10f** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **10g** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **10h** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **10i** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **10j** | 0 | 0 | 0 | 0 | 0 | 0 |

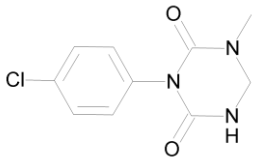
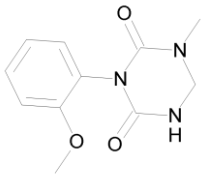
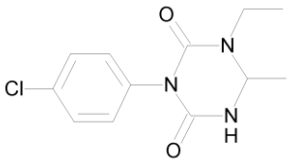
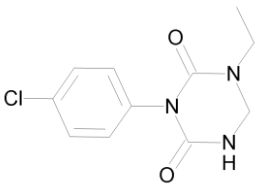
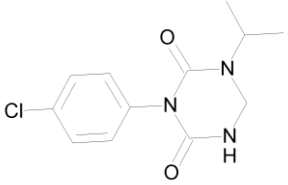
### 5.4. Biological evaluation of *N,N'* dialkyl triazolidine-3,5-diones

This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of *N,N'*-dialkyl triazolidine-3,5-dione derivatives. Herbicidal activities of some *N,N'*-dialkyl triazolidine-3,5-dione compounds are tabulated below:

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| Structure | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **11a** | 90 | 90 | 90 | 70 | 70 | 70 |
|  **11f** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **11g** | 90 | 70 | 80 | 20 | 50 | 35 |
|  **11h** | 20 | 0 | 10 | 0 | 0 | 0 |
|  **11i** | 0 | 0 | 0 | 0 | 0 | 0 |

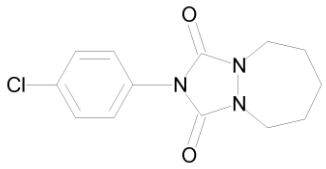
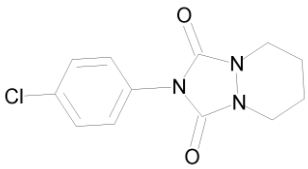
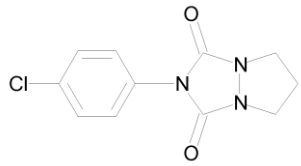
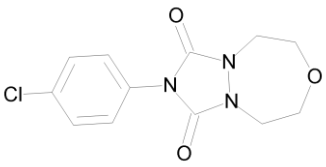
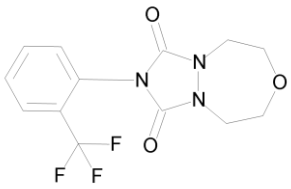
### 5.5. Biological evaluation of dihydro triazine-2,4-diones and their derivatives

This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of dihydro triazine-2,4-diones and their derivatives. Herbicidal activities of some dihydro triazine-2,4-diones and their derivatives are tabulated below.

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| Structure | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **14a** | 50 | 0 | 25 | 0 | 0 | 0 |
|  **14f** | 0 | 0 | 0 | 0 | 0 | 0 |
|  **14m** | 70 | 50 | 60 | 0 | 0 | 0 |
|  **14o** | 70 | 50 | 60 | 0 | 0 | 0 |
|  **14p** | 90 | 90 | 90 | 50 | 50 | 50 |

### 5.6. Biological evaluation of bicyclic triazolidine-3,5-diones

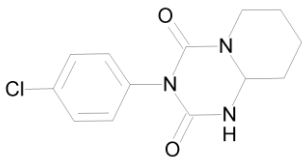
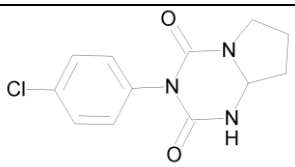
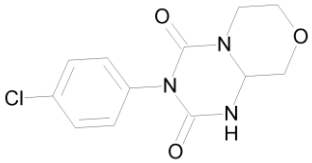
This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of bicyclic triazolidine-3,5-dione derivatives. Herbicidal activities of some bicyclic triazolidine-3,5-diones and their derivatives are tabulated below:

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| Structure | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **18a** | 90 | 90 | 90 | 90 | 90 | 90 |
|  **18b** | 90 | 90 | 90 | 90 | 90 | 90 |
|  **18c** | 90 | 90 | 90 | 90 | 90 | 90 |
|  **18d** | 90 | 90 | 90 | 90 | 90 | 90 |
|  **18e** | 0 | 0 | 0 | 0 | 0 | 0 |

### 5.7. Biological evaluation of N–C bridgehead heterocycles

This section describes the biological assay and fungicidal, insecticidal, herbicidal activities of N–C bridgehead heterocycles.

Herbicidal activities of some N–C bridgehead heterocycles are tabulated below:

| **Herbicidal Assays** | | | | | | |
|---|---|---|---|---|---|---|
| | *Arabidopsis thaliana* | | | *Digitaria sanguinalis* | | |
| | Herbicide effect | | | Herbicide effect | | |
| Structure | Rep 1 | Rep 2 | Avg | Rep 1 | Rep 2 | Avg |
|  **19a** | 90 | 90 | 90 | 70 | 70 | 70 |
|  **19b** | 70 | 90 | 80 | 70 | 70 | 70 |
|  **19d** | 20 | 0 | 10 | 70 | 70 | 70 |

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# List of Publications

## A] In National/International Journals

1. "Synthesis of unsymmetrical dihydro triazine-2,4-diones via a Grob-like N–N fragmentation of urazoles followed by intramolecular cyclization" **Subhaskar R. Panga,** Roger G. Hall, Rashmi V. Samant, Mark Montgomery, Ashok Shyadligeri. *Tetrahedron Lett.* **2022,** *106***,** 154076.

2. "Synthesis of N–C Fused Bicyclic 1, 3, 5-Triazinane-2, 4-dione Derivatives from Saturated Ring-Fused Urazoles" **Subhaskar R. Panga,** Roger G. Hall, Ashok Shyadligeri, Shrikant A. Shete, Bhanu N. Manjunath. *Synlett* **2023**, *34*, 353-358.

## B] In National/International Conference Proceedings

1. "Access to a new class of dihydro 1,3,5-triazine-2,4-dione bicyclic compounds *via* fragmentation followed by simultaneous ring expansion-contraction of bicyclic triazolidinediones" **Subhaskar R. Panga,** Roger G. Hall, Shrikant A. Shete, Ashok Shyadligeri. Presented a poster in the Three-Day National Conference at 29$^{th}$ CRSI National Symposium in Chemistry (CRSI-ACS Symposium Series in Chemistry) held at IISER Mohali, Punjab during 07$^{th}$ - 09$^{th}$ July 2022. **Abstr. No: P-279.**

2. Participated in two-day virtual international conference on "Advances on Green Chemistry and Sustainable Technology", which was held on 29$^{th}$ and 30$^{th}$ September 2021 and organized by Dnyanprassarak Mandal's College and Research Centre, Goa, in association with Syngenta Biosciences Pvt Ltd.

3. Participated in a conference on "Syngenta Agroscience Symposium: Sustainable chemistry and technology" held on 4$^{th}$ Nov 2019, which was organized by Syngenta Biosciences Pvt Ltd, Goa.

4. Participated in international conference on “EMERGING TRENDS IN CHEMSTRY” held on 12$^{th}$ – 15$^{th}$ July 2019, which was organized by Indian Institute of Technology Indore, Indore.

| | |
|---|---|
| Subhaskar Reddy Panga | Dr. Bhanu N. Manjunath |
| (Research student) | (Research Guide) |